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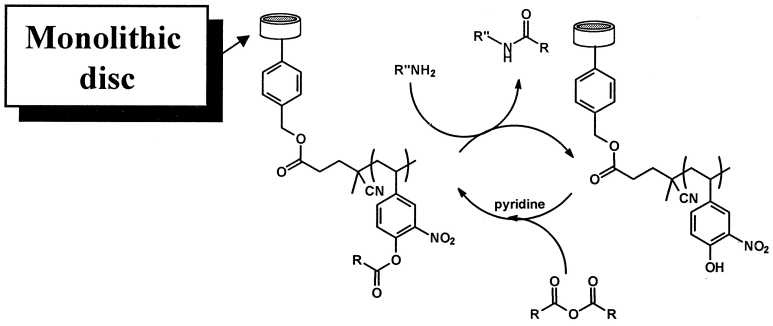

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Solid-Phase Acylating Reagents in New Format: Macroporous Polymer Disks

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Acylation resins in a new monolithic format have been prepared by the functionalization of polyethylene-encased porous poly(chloromethylstyrene-*co*-divinylbenzene) disks. These disks have been obtained from a monolithic rod prepared by polymerization in a cylindrical glass mold, then cut into a disk format. A free radical azo initiator 4,4′-azobis(4-cyanovaleric acid) attached to available chloromethyl functionalities at the surface of the pores was used to initiate graft polymerization of 4-acetoxystyrene or chloromethylstyrene from the surface. Addition of a small percentage of divinylbenzene to the polymerization mixture leads to the formation of a layer of swellable reactive polymer gel at the surface of the macropores. This both prevents the undesirable increase in flow resistance through the monolith and improves the yield of grafting. The final reaction steps involve formation of an active phenolic moiety grafted to the disks and its reaction with acid anhydride. The use of grafted disks as acylating resin to transform various amines to amides in flow-through operations is demonstrated in a variety of solvents including alcohols. The acylation ability of the depleted disks can easily be recovered, and the disks can be reused many times.

Introduction

Combinatorial chemistry has undergone an enormous increase in popularity because of the large numbers of compounds that can be rapidly prepared and screened for their properties. Typically, the solid phase as developed by Merrifield in 1963[1] is used as a support for a covalently bound starting compound, which is first transformed to the desired product and then cleaved from the support. This approach is favored because it facilitates product workup after each reaction step, reducing it to a mere filtration and enabling the fast preparation of compounds.[2] However, the number of available reactions on solid phases is currently limited. In contrast, the variety of solution-phase reactions is virtually endless, and therefore, the solution-phase approach to library preparation is more versatile. The major weakness of solution-phase synthesis, the tedious purification steps that are usually required along the reaction path, may be addressed by using insoluble reactive polymers in polymer-assisted solution-phase (PASP) reactions.[3] For example, these polymers can be used as scavengers to remove impurities or excess reagents from solutions, leaving the purified product in solution. Another PASP approach relies on polymers bearing reactive groups that can effect a transformation of molecules in solution.[4] Because these polymeric reagents can be used in excess, the reactions may be driven to completion and the excess polymeric reagent can later be removed simply by filtration. A number of acylating resins such as polymer-bound anhydrides,[5] dithiocarbamic anhydrides,[6] derivatives of 2,3,5,6-tetrachlorohydroquinone,[7] oximes,[8] *N*-trifluoroacetyl-nylon 66,[9] oximino esters,[10] and derivatives of 4-hydroxy-3-nitrobenzophenone[11] have been studied.

The vast majority of polymers used in PASP reactions to date are prepared and used in the shape of beads. This format is often preferred because the preparation of beads using suspension polymerization is simple and well worked out for the wide range of chemistries. As a result, beads containing a range of reactive groups are commercially available.[12] The continuing quest for acceleration of combinatorial synthesis requires extensive automation of processes in which the precise handling of beads of varying sizes may become difficult. As a result, new formats of polymer supports have recently emerged. For example, we reported the preparation of modified macroporous polymer monoliths in the shape of disks for use as polymeric scavengers to remove excess amines from solutions in a technique called "reactive filtration".[13] Similarly, Sherrington and co-workers used swellable polymer disks as a support for solid-phase synthesis,[14] and Janda prepared monolithic gel supports in a variety of Euclidean shapes.[15] In addition to the facilitated handling of these macroscopic objects, the monolithic formats that we have developed can be easily used in a flow-through mode that accelerates mass transfer within the pores, thus allowing considerable reduction in contact times to achieve the same extent of reaction as with typical beads.

In this communication we report the preparation and use of monolithic disks with activated ester functionalities that extend the previous function of disks from that of passive scavenging component[13] to that of a polymer-supported reagent that actively participates in the reactions.

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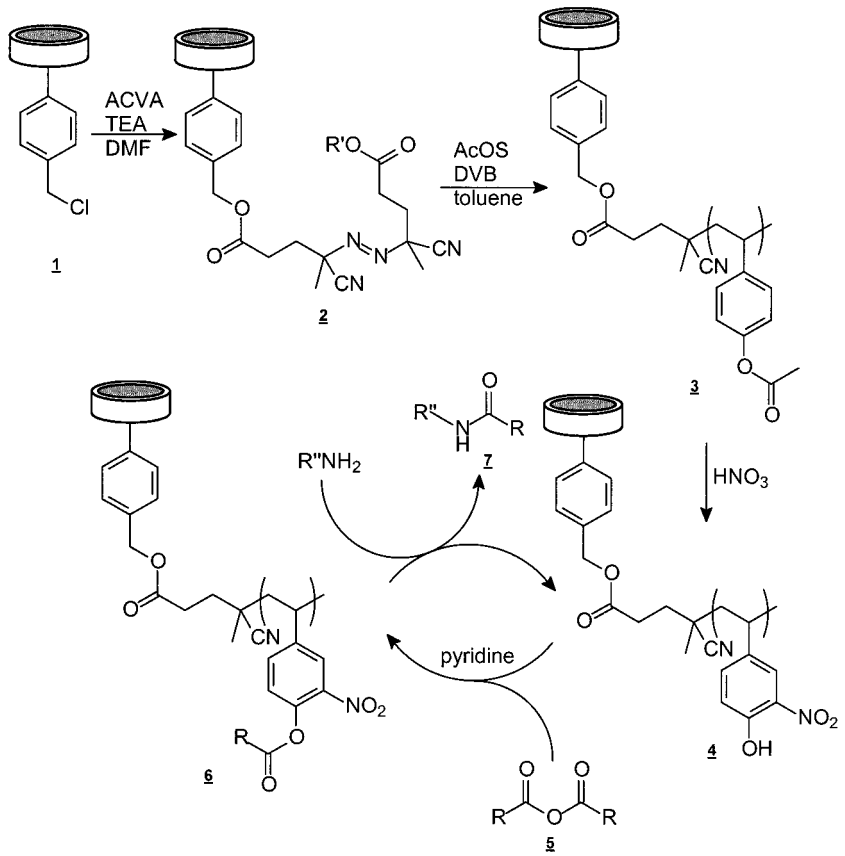
Scheme 1



Results and Discussion

Preparation of the Monolithic Disks. As described in detail in our previous work,[13] the monoliths were prepared in an unstirred mold by bulk polymerization of a mixture that included a functional monomer (chloromethylstyrene), cross-linker (divinylbenzene), and free radical initiator (2,2′-azobis(isobutyronitrile)) dissolved in porogenic solvents (toluene and dodecanol) at 70 °C. This polymerization affords a unique pore size distribution quite dissimilar to that of macroporous beads prepared from a mixture of equal composition.[16] The monolithic materials typically contain both small pores that contribute to the surface area and large pores that facilitate flow through the monolith. To increase their mechanical stability and simplify their handling, the monoliths used in this study were prepared as cylinders with a diameter of 12 mm encased in shrinkable polyethylene tubing for a final diameter of 14 mm. The polyethylene sheath protects the edges of the monolith, allowing it to be cut into disks about 5 mm thick.[13] The tubing also helps to seal the monolith in the cartridge used for reaction as solutions flow through the monolith rather than escaping from its edges.

Monolith-Supported Nitrophenyl Esters. The preparation of the polymeric acylation reagent is shown in Scheme 1. The benzylic chloride group of poly(chloromethylstyrene-*co*-divinylbenzene) (CMS−DVB) monolith **1** serves as a handle for further functionalization. First, the CMS−DVB monolith is reacted with 4,4′-azobis(4-cyanovaleric acid) (ACVA), an azo initiator containing reactive carboxylic acid functionalities via displacement of the halogen of the benzyl chloride groups located at the pore surface and forming an ester bond. In addition, the nitrogen content of the monolithic disks increases from 0 to about 0.7% (after heating to remove nitrogen gas), suggesting the incorporation of about 0.5 mmol/g of initiator functionalities. The pores of the functionalized monolith **2** are then filled with a toluene solution of 4-acetoxystyrene (AcOS) containing 1% divinylbenzene with respect to the monovinyl monomer and heated to initiate grafting. The addition of cross-linker ensures that all monomers introduced into the pores form a gel grafted at the surface of the pores of the monolith. The slight cross-linking of the grafted layer also decreases the flow resistance of the overall monolithic structure.[13] Although the amount of grafted polymer cannot be directly quantified using elemental analysis, a weight increase of 0.055 g is seen for a disk with an original mass of 0.424 g. This value matches exactly the expected weight increase, indicating complete incorporation of the monomer into the grafted gel. The IR spectrum of the grafted polymer **3** shows a carbonyl peak at 1760 cm^{-1} and confirms the presence of polymerized AcOS moieties. As demonstrated in our previous work,[13] there is little change in the porous properties of the monoliths before and after grafting.

We discussed in our previous work[13] that the amount of grafted polymer must balance the need for high capacity with that for unobstructed flow through the monolith. This is achieved by grafting using a 20% monomer solution, affording disks with a functionalization of 0.3−0.5 mmol/disk.

To prepare the polymeric reagent, the poly(4-acetoxystyrene) units are activated by submerging the grafted monolithic disks in concentrated nitric acid for 30 min, thereby effecting nitration of the aromatic rings (Scheme 1).

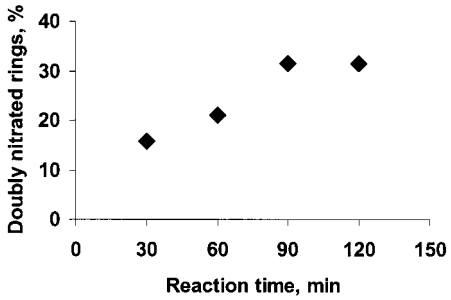


Figure 1. Effect of reaction time on multiple nitration of grafted acetoxystyrene moieties. Reaction conditions are the following: disk grafted with a solution of 20% 4-acetoxystyrene and 0.4% divinylbenzene in toluene; nitration in concentrated nitric acid; extent of nitration calculated from elemental analysis of nitrogen.

Since the number of nitro groups present in the product, as determined by elemental analysis of nitrogen, exceeds the number of grafted AcOS rings, it is likely that some phenyl groups are nitrated in both the 3- and 5-positions. Therefore, the nitrogen content of the monoliths after nitration is found to be 2.9%. This exceeds the value of 2.6% that would be obtained by incorporation of nitrogen through the nitrile groups of the initiator (0.7%) and through mononitration of the acetoxystyrene residues (1.9%). This finding suggests that about 15% of the rings bear two nitro groups. Figure 1 shows that increasing the reaction time of the nitration to 120 min does not significantly increase the extent of nitration. Figure 2 shows the IR spectra of both the original monolith **3** and its nitrated counterpart **4**. Clearly, the peak of C═O stretch vibrations at 1760 cm^{-1} corresponding to the acetyl group disappears as the phenolic ester groups are cleaved to the free phenol during the nitration reaction. In contrast, the band at 1735 cm^{-1} corresponding to the benzylic ester bond that links the polymer gel to the surface of the monolith remains intact. Finally, the absorption bands of the nitro group can be clearly seen in the IR spectrum of Figure 2b at 1554 and 1341 cm^{-1}.

The last step in the preparation of the monolith-supported acylating reagent is the attachment of the desired acyl group to nitrated polymer **4**. This is easily achieved by reaction of monolith **4** with a carboxylic acid anhydride **5** in the presence of pyridine. The carbonyl band is again clearly seen in the IR spectrum at 1760 cm^{-1}. Disappearance of the phenolic O−H band from the IR indicates that all of the phenolic groups have reacted, leading to an acyl groups capacity of 0.71 mmol/g or 0.34 mmol/disk. This value is consistent with the observed reactivity.

Monolith-Supported Tetrachlorophenyl Esters. An alternative monolith-supported acylating reagent with chemistry based on 2,3,5,6-tetrachlorohydroquinone (TCHQ) was prepared using the reaction path shown in Scheme 2. Once again the starting material is the CMS−DVB monolith **1** functionalized with the ACVA free radical initiator. The pores of monolith **2** are then filled with a solution of chloromethylstyrene (CMS) in toluene containing divinylbenzene (1% in respect to the monovinyl monomer) and heated to achieve complete polymerization of the monomers. Grafting of the CMS is necessary in order to increase the amount of reactive benzylic chloride groups of the original monolith. The weight increase upon grafting is similar to that observed from grafting 4-acetoxystyrene. As expected, the size of the characteristic benzylic chloride IR peak at 1265 cm^{-1} increases during this reaction. The halogen atoms of the benzylic chloride moieties located in the grafted gel were displaced by reaction with a *N*,*N*-dimethylformamide

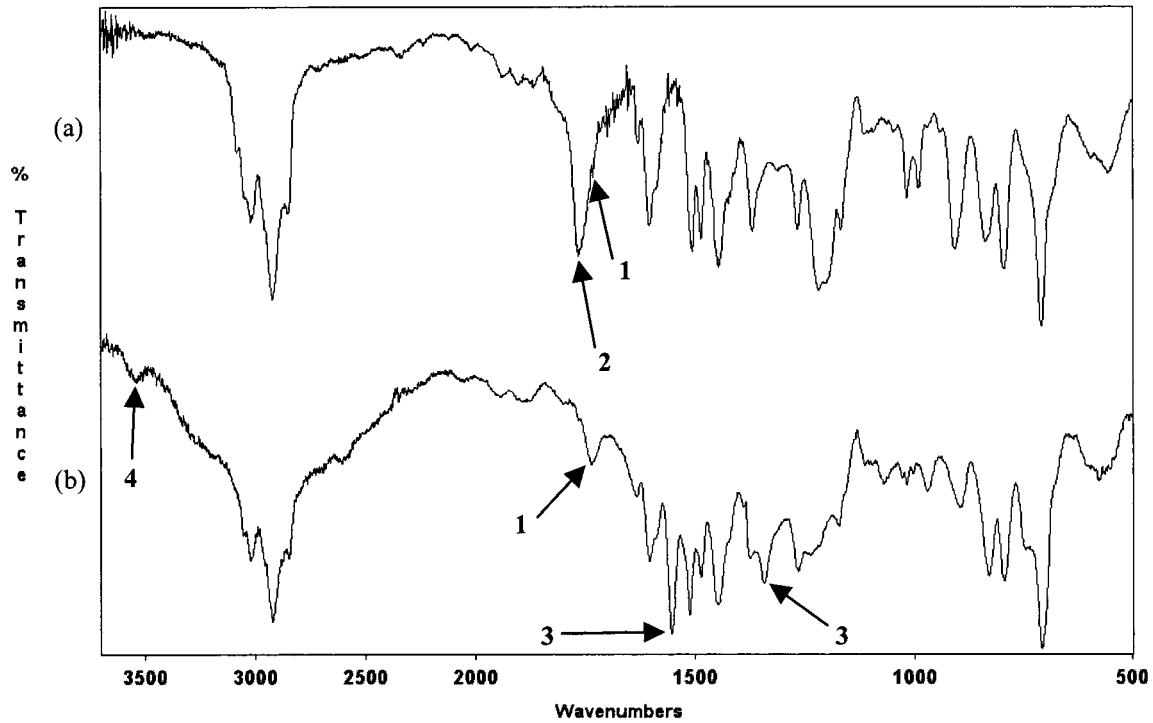
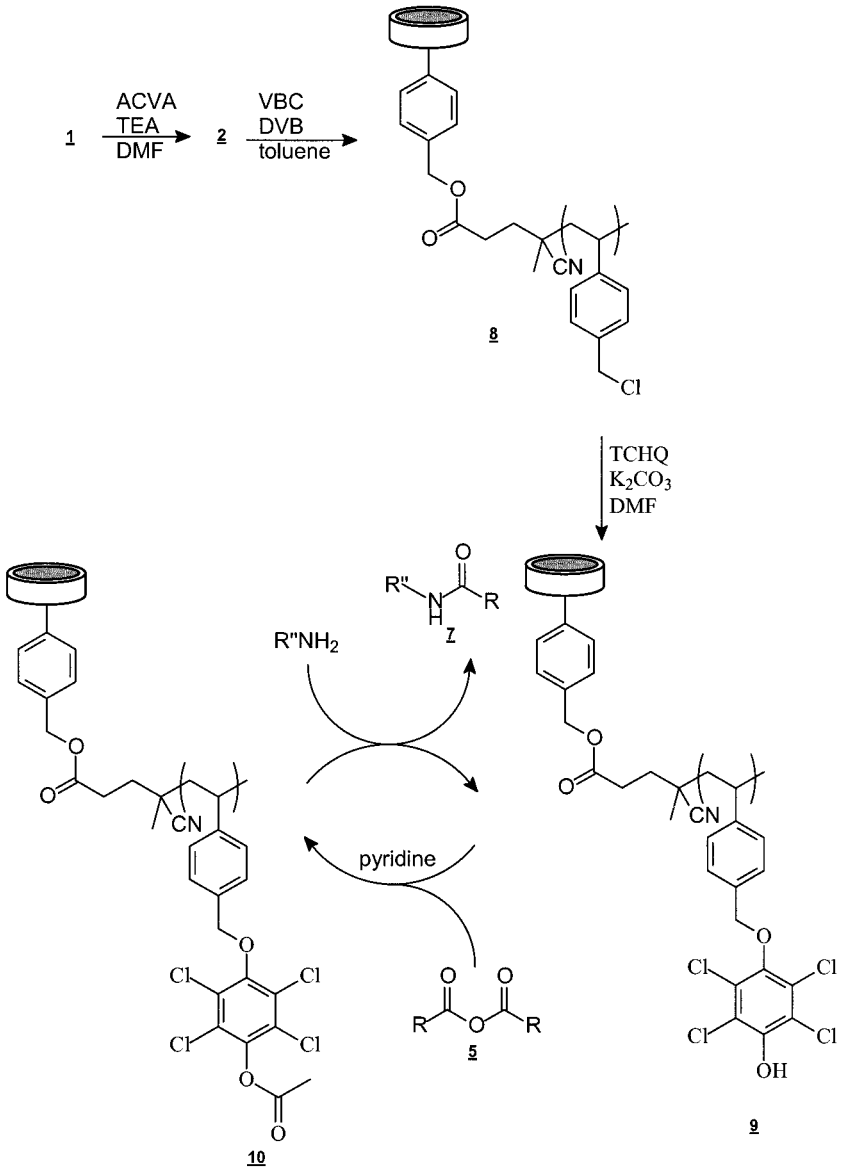


Figure 2. Infrared spectra of monolithic disks grafted with poly(4-acetoxystyrene) before (a) and after (b) 30 min nitration: (peak 1) 1735 cm^{-1}, carbonyl group of ester linking the grafted polymer to the monolith; (peak 2) 1760 cm^{-1}, carbonyl group of acetyl originating from grafted poly(4-acetoxystyrene); (peak 3) 1554 and 1342 cm^{-1} nitro groups; (peak 4) 3540 cm^{-1}, hydroxyl groups of substituted phenol moieties.

Scheme 2



solution of TCHQ in the presence of potassium carbonate to afford polymer **9**. The capacity of this monolith as determined from the elemental analysis for chlorine is 0.8 mmol/g or about 0.4 mmol/disk. The IR spectrum of the product of this reaction now shows a new peak at 3500 cm^{-1} corresponding to the phenolic groups. Acylation by reaction with acetic anhydride in pyridine leads to a monolith-supported activated ester **10** with a carbonyl peak at 1785 cm^{-1} in its IR spectrum.

Acylation with Monolith-Supported Reagents. The advantage of using monolithic disks instead of an array of beads is that solutions can be pumped *through* the monolith. This convective transport of reagents to the reactive sites is faster than the slow diffusion process that must occur within the pores of typical beads. To achieve the desired flow of solutions through the monolith, the grafted monolithic disks were encased in a polyethylene ring and inserted into the custom-made holder described previously.[13]

To conduct the acylation reactions using the supported reagent, a solution of amine in a specific solvent was pumped though the monolith using a pulseless syringe pump, and gas chromatographic analysis was used to determine the amount of reacted amine. An example of GC monitoring of benzylamine uptake in samples taken before and after passage through a monolithic acetylating reagent is shown in Figure 3. Approximately a 3-fold excess of acylating groups was used in this experiment. A large benzylamine peak is clearly visible in the sample of the original solution. This peak is almost invisible after a reaction time of 8.0 min, while a peak with a retention time of 4.27 min corresponding to the *N*-benzylacetamide can be seen. GC analysis indicates a conversion of 99.3% based on the disappearance of amine.

Figure 4 shows that the extent of the reaction depends on the residence time of the amine inside the pores of the monolith. The residence time can easily be controlled by altering the rate at which the amine solution flows through the monolith. Clearly, a longer residence time allows more of the amine to react. For example, approximately 74% of the amine is consumed after a residence time of 1.0 min achieved at a flow rate of 24.0 mL/h. An increase of the residence time to 8.0 min at a flow rate of 3.0 mL/h affords

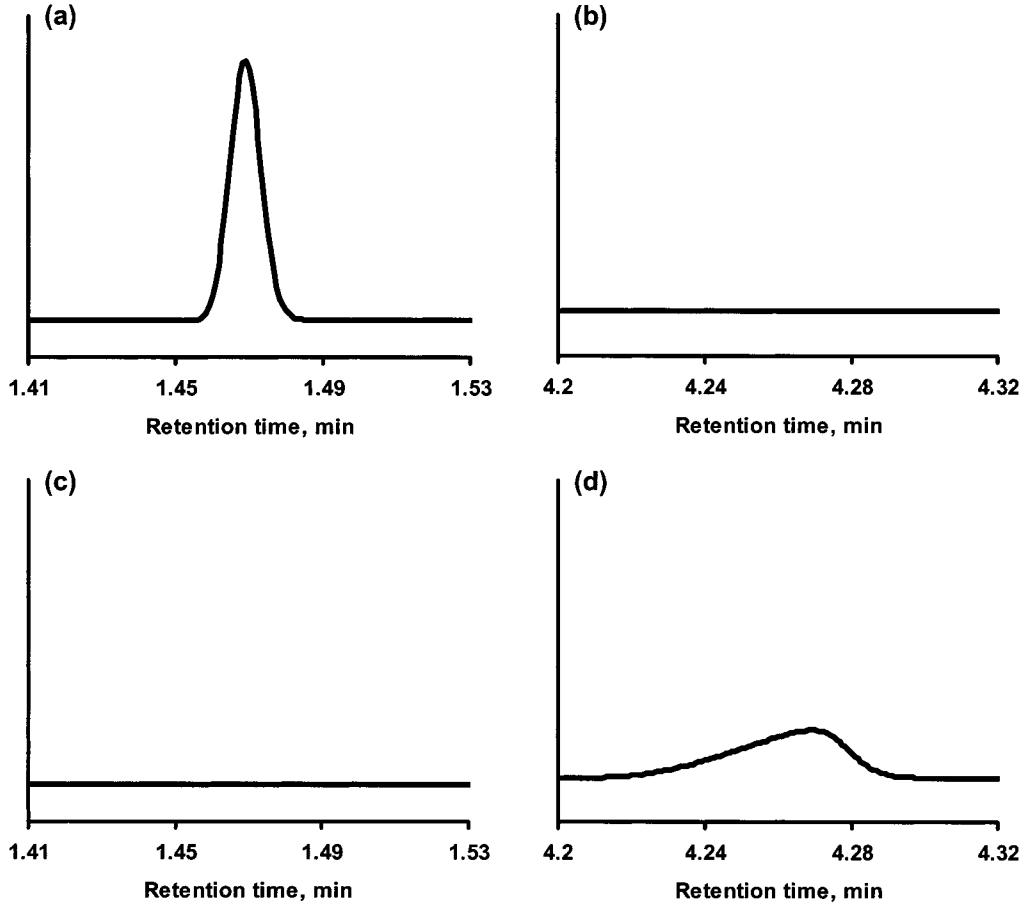


Figure 3. Gas chromatographic analysis of reaction solutions before and after passing the monolithic acetylating disk. Reaction conditions are the following: grafted disk nitrated for 30 min and acylated with 1:1 acetic anhydride/pyridine for 20 h; solution of 0.1 mmol of benzylamine in 1.5 mL of THF; flow rate of 3.0 mL/h; residence time of 8.0 min. (a) Amine peak in the original solution before the acylation reaction. (b) Location of amide peak before reaction. (c) Location of amine peak after acylation reaction. (d) Amide peak after reaction. Overall conversion is 99.3%.

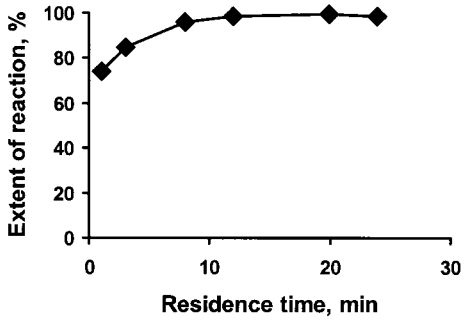


Figure 4. Effect of residence time on conversion. Reaction conditions are the following: disk grafted with a solution of 20% 4-acetoxystyrene and 0.4% divinylbenzene in toluene; nitration time of 30 min; acylation with 1:1 acetic anhydride/pyridine for 20 h; solutions of 0.1 mmol of benzylamine in 1.5 mL of tetrahydrofuran were pumped through disk at various flow rates.

about 99% conversion. This result confirms again[13b] that the flow-through implementation of these reactions enhances reaction rate and leads to high conversions at shorter reaction times compared to more common bead-supported reagents. Typically reaction mixtures containing these beads must be maintained for several hours to achieve an extent of reaction comparable to that obtained with the monolith in less than 1 h. In addition, the flow-through mode allows the cartridge containing the disk to be easily attached to a pump and used in an automated system.

Table 1. Preparation of Acetamides from Various Amines Using Monolithic Acylating Disk[a]

amine[b]	solvent	conversion,[c] %
benzylamine	tetrahydrofuran	99.3
butylamine	dichloromethane	89.9
phenethylamine	tetrahydrofuran	99.7
diethylamine	dichloromethane	97.4
3,5-dimethylaniline	tetrahydrofuran	49.2

[a] Disk grafted with a solution of 20% 4-acetoxystyrene and 0.4% divinylbenzene in toluene; flow rate of 3.0 mL/h; residence time of 8.0 min. [b] Solution of 0.1 mmol of amine in 1.5 mL of solvent. [c] Conversion determined by GC.

The general effectiveness of the solid-phase acylation reagent was demonstrated using a variety of amines. As expected, the reactivity of the specific amine relates to its nucleophilicity. Table 1 shows that the monolithic reagent affords conversions close to 100% after 8 min of reaction time with both nonaromatic primary and secondary amines. In contrast, the conversion of the acylation reaction with 3,5-dimethylaniline, which is a poor nucleophile, is less than 50% under identical conditions.

The nitrated polymer-bound phenol moieties react with a variety of acid anhydrides to form a number of different acylation reagents. Table 2 shows a few examples of various groups used to acylate benzylamine. Most of the reagents are very reactive, affording conversions over 98% after only

Table 2. Acylation of Benzylamine Using Various Monolithic Solid-Phase Reagents[a]

R[b]	conversion,[c] %
methyl	99.3
ethyl	98.7
i-propyl	100
tert-butyl	93.4
hexyl	100
phenyl	100

[a] Reaction conditions: monolith disk grafted with a toluene solution of 20% 4-acetoxystyrene and 2% divinylbenzene, nitrated and activated; 0.1 mmol of benzylamine solution in 1.5 mL of tetrahydrofuran; flow rate of 3.0 mL/h, residence time of 8.0 min. [b] R is the substituent of the acyl group that was attached to the nitrophenol moiety of the grafted disk by reaction with specific carboxylic acid anhydride in pyridine solution. [c] Conversion of amine determined by GC.

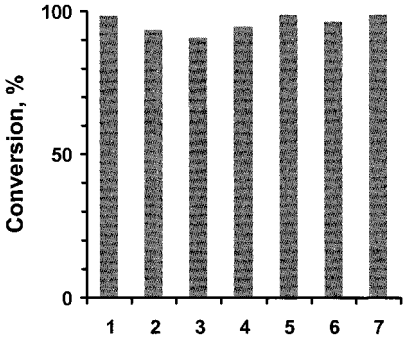


Figure 5. Regeneration of acylating activity. Reaction conditions are the following: disk grafted with a solution of 20% 4-acetoxystyrene and 0.4% divinylbenzene in toluene; nitration time of 30 min; acylation with 1:1 acetic anhydride/pyridine for 20 h; solutions of 0.1 mmol benzylamine in 1.5 mL of tetrahydrofuran pumped through disk at a flow rate of 3.0 mL/h; residence time of 8.0 min; regeneration after each reaction by submersion of the disk in 50% pyridine solution of acetic anhydride for 20 h.

8 min of residence time. The slightly lower conversion observed for *tert*-butyl ester can be ascribed to steric effects.

The acylating moiety of the monolith-supported reagent can be easily regenerated by reattaching the desired acyl group through treatment of the disk in situ with a solution of anhydride and pyridine. This process does not lead to any decrease in acylation efficiency. This is demonstrated through the reaction of benzylamine with the polymer-supported reagent followed by reactivation with acetic anhydride. As shown in Figure 5, no loss in reactivity is observed even after seven consecutive acetylation−reactivation cycles.

All of the reactions described above have been carried out in tetrahydrofuran or dichloromethane as solvents. Surprisingly, the acylation reaction also proceeds fairly well in protic solvents such as 2-propanol. For example, the acetylation of benzylamine in 2-propanol affords a conversion of 89.9% in 8 min. The IR spectrum of the monolithic polymer taken after reaction indicates the presence of unreacted acetyl groups. This suggests that the polymeric reagent is not readily quenched with the alcohol. Only a very small peak corresponding to less than 5% 2-propyl acetate is detected in the GC.

The alternative monolith-supported acylation reagent **10**, based on tetrachlorohydroquinone chemistry (Scheme 2), was tested under conditions similar to those for the nitrophenol-type reagent **7**. Results achieved with both types of monolith-supported reagent are fully comparable. For example, the acetylation of benzylamine with the TCHQ-based disk in THF affords a conversion of 96.2% after 8.0 min of residence time.

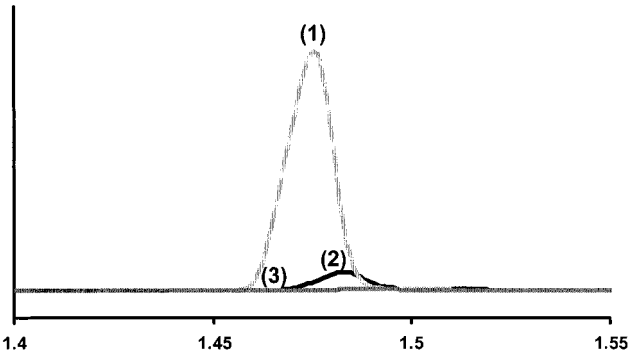


Figure 6. Gas chromatograms of reaction solutions before reaction (1), after reaction using only acetylating disk (2), and after reaction using both acetylating and scavenging disks in series (3). Reaction conditions are the following: acylating disk grafted with a solution of 20% 4-acetoxystyrene and 0.4% divinylbenzene in toluene; nitration time of 30 min; acylation with 1:1 acetic anhydride/pyridine for 20 h; scavenging disk grafted with a solution of 20% 4,4-dimethyl-2-vinylazlactone and 0.2% divinylbenzene in toluene; solutions of 0.3 mmol benzylamine in 1.5 mL of tetrahydrofuran pumped through disk at a flow rate of 3.0 mL/h; residence time of 8.0 min.

Combination of Reaction and Scavenging in a Single Step. The construction of the disk holder allows the use of several disks stacked on top of each other. Clearly, the use of more than one acylating disk can increase the overall reaction capacity of the system. In addition, this also enables the simultaneous use of disks with different chemistries. This is demonstrated by a combination of acylation and scavenging to ensure the preparation of a pure amide.

For this demonstration, we used a single acetylating disk containing nitrophenyl ester functionalities that reacted with benzylamine under conditions for which 86% conversion is achieved and 14% of the original amine remains in solution together with the amide. Trace 1 in Figure 6 is the GC chromatogram of the amine solution prior to reaction with the acylating disk. Trace 2 represents the amine solution after being passed through a single acylating disk containing an equimolar amount of acylating moieties with respect to the amine. Because conversion is 86%, a peak for benzylamine can still be seen. A peak corresponding to the amide is also seen at a retention time of 4.27 min. However, once another disk-grafted poly(2-vinyl-4,4-dimethylazlactone) is placed downstream, it scavenges all of the residual benzylamine and no amine peak at 1.47 min can be seen (GC trace 3), indicating that all remaining free amine has been scavenged. This purification is readily achieved because the chemistries of the two disks are strictly segregated and do not interfere with each other. It should be emphasized that this binary reaction in a single path cannot be accomplished with beads functionalized with relevant chemistries admixed to an amine solution because both types of beads (reagent and scavenger) would compete for the amine at the same time and the yield as well as purity of the desired amide would be compromised.

Conclusion

Polymer-supported reagents prepared in a macroscopic disk format are a useful alternative to the more common bead-supported reagents. These disks are obtained by modification of a porous polymer monolith through the grafting of a coating of reactive polymer gel at the surface of their very large pores. The disks operate in a flow-through mode that accelerates mass transfer, requiring much shorter reaction times to achieve almost complete conversions. In addition, the use of such macroscopic objects that can be handled individually can facilitate automation of processes in which polymer-supported reagents are used. The disk technology also enables the use of disks with different chemistries in series. Because the chemistries of these disks are spatially separated, it is possible to achieve several consecutive chemical transformations in a single path. The approach demonstrated in this report is general and can be easily extended to a number of monoliths with a broad variety of functional groups.

Experimental Section

Materials. Chloromethylstyrene (CMS) (a mixture of 3- and 4-isomers) was purchased from Dow Chemical and 4-acetoxystyrene (AcOS) was purchased from Aldrich. 4,4′-Azobis(4-cyanovaleric acid) was purchased from Aldrich and purified by repeated washing with diethyl ether. Divinylbenzene (DVB, Aldrich, 80% grade) was a mixture of isomers containing ethylvinylbenzenes as the major impurities. 2,3,5,6-Tetrachlorohydroquinone was obtained from Sigma. It was recrystallized prior to use. All other reagents were obtained from Aldrich and used as supplied.

Instrumentation. IR spectra were taken on a Mattson Genesis II FTIR spectrometer using the total reflectance mode. Porous properties of the polymers were measured using a Micromeritics Autopore 9420 mercury intrusion porosimeter. Gas chromatography was carried out using an HP 6890 series GC system equipped with an autoinjector and 30 m HP-5 column. The data were acquired and processed with HP GC ChemStation software.

Preparation of Poly(chloromethylstyrene-*co*-divinylbenzene) Monoliths. The monoliths were prepared in molds consisting of a 14 mm i.d. glass tube sealed at one end and containing walls lined with a shrinkable polyethylene tubing.[13] 2,2′-Azobis(isobutyronitrile) (0.12 g, 1 wt % with respect to monomers) was dissolved in a solution of CMS (4.8 g), DVB (7.2 g), toluene (5.25 g), and 1-dodecanol (12.75 g). The mixture was purged with nitrogen for 10 min, the mold was filled with this mixture, and its open end was then sealed using a rubber septum secured with wire and adhesive tape. The polymerization was allowed to proceed in a thermostated bath for 20 h at 70 °C. The glass tube was then carefully crushed, and the monolith, tightly embraced by the polyethylene tubing, was removed and sliced into 5 mm thick disks using a table saw. These disks were extracted with THF for 24 h in a Soxhlet apparatus. Elemental analysis: 9.67% Cl (2.7 mmol/g benzyl chloride groups).

Attachment of 4,4′-Azobis(4-cyanovaleric acid) to Monolith Surface. To a solution of 3.33 g of ACVA and 2.22 g of triethylamine in 6.66 mL of *N*,*N*-dimethylformamide in a reaction flask were added several monolithic CMS−DVB disks. The reaction was carried out without stirring at room temperature for 48 h. The modified disks were then extracted with diethyl ether in a Soxhlet extractor for 24 h. IR: 1735 cm^{-1} (C═0). For characterization purposes and prior to elemental analysis, the monolithic disks were submerged in toluene and heated to 70 °C for 20 h to remove the diazo groups, followed by washing with THF to remove any unattached compounds. Elemental analysis of nitrogen after this heating: 0.69% N, or 0.5 mmol/g of initiating species.

Grafting of 4-Acetoxystyrene. The monolithic disks functionalized with a free radical initiator were submerged in a toluene solution containing 20 wt % AcOS and 2% DVB (weight with respect to that of AcOS). The mixture was purged with nitrogen for 10 min, and the flask was sealed and heated in a bath to 70 °C for 20 h. The soluble polymer was removed from the grafted disks by extraction with THF in a Soxhlet apparatus for 24 h. Any polymer gel on the outside surface of the monolith was removed mechanically using a razor blade. IR: 1760 cm^{-1} (C═O). The weight increase of 0.055 g/disk corresponds to essentially complete incorporation of the monomer.

Nitration of Disks Grafted with 4-Acetoxystrene. Monolithic disks grafted with AcOS gel were completely submerged in concentrated nitric acid for 30 min. They were then washed thoroughly with water, then washed with triethylamine, and extracted with methanol in a Soxhlet apparatus for 24 h. IR: 1554, 1341 cm^{-1} (NO_2); 1735 cm^{-1} (C═O from attached initiator); 3247 cm^{-1} (phenolic OH). Elemental analysis: 2.87% N.

Formation of Activated Acetic Acid Ester. A monolithic disk containing grafted nitrophenol groups was submerged in a 1:1 solution of acetic anhydride in pyridine and allowed to react without stirring for 20 h. After reaction, the disk was extracted with THF in a Soxhlet apparatus for 24 h. IR: 1760 cm^{-1} (ester C═O).

Formation of Other Activated Esters. Monolithic disks containing grafted polymer gel with nitrophenol groups were submerged in a solution of the appropriate anhydride in pyridine and allowed to react without stirring for 150 h. The disks were then extracted with THF in a Soxhlet apparatus for 24 h.

Grafting of Vinylbenzyl Chloride. The monolithic disks functionalized with free radical initiator were submerged in a toluene solution containing 20 wt % CMS and 2% DVB (wt % with respect to CMS). The mixture was purged with nitrogen for 10 min, and the flask was sealed and heated in a bath to 70 °C for 20 h. The soluble polymer was removed from the grafted disks by extraction with THF in a Soxhlet apparatus for 24 h. Any polymer gel on the outside surface of the monolith was removed mechanically using a razor blade. IR: 1265 cm^{-1} (benzyl−Cl). Elemental analysis: 12.33% Cl (1.2 mmol/g additional benzylic chloride groups).

Attachment of 2,3,5,6-Tetrachlorohydroquinone. A monolithic disk grafted with CMS gel was submerged in a solution of 0.5 g (2.0 mmol) of 2,3,5,6-tetrachlorohydroquinone (TCHQ) and 0.18 g (1.3 mmol) of potassium carbonate in 1.75 mL of *N*,*N*-dimethylformamide. The solution was heated at 70 °C for 36 h and then washed with

THF in a Soxhlet apparatus for 24 h. IR: 1368 cm^{-1} (phenol C−O); 3500 cm^{-1} (phenol O−H); 710 cm^{-1} (aromatic C−Cl); 1265 cm^{-1} (benzyl−Cl); 1735 cm^{-1} (C═O from initiator). Elemental analysis: 15.32% Cl (0.8 mmol/g TCHQ groups).

Formation of TCHQ-Based Activated Esters. A monolithic disk containing grafted polymer gel with TCHQ groups was submerged in a solution of acetic anhydride in pyridine and allowed to react without stirring for 150 h. The disk was then extracted with THF in a Soxhlet apparatus for 24 h. IR: 1785 cm^{-1} (C═O).

Acylation of Amines Using Monolithic Supported Reagents. The monolithic disk was placed in a custom-made stainless steel holder and attached to a syringe pump (KD Scientific model 101). In a typical reaction, the monolith was first washed with the desired solvent, and then the solution containing the amine to be reacted was pumped through the monolith at a specific flow rate. After the reaction was completed, the monolith was washed again with the solvent. The difference in composition of the solutions, determined before and after reaction by means of gas chromatography, was used to estimate the amounts of amine that had reacted.

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